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(54) Title: REDUCTION OF UV INDUCED SKIN CANCER BY TOPICAL AMINES

(57) Abstract

The present invention provides a pharmaceutical composition in the form of an excipient in combination with an aminothiol or an aryl amide to prevent UV induced skin cancer. Further, the invention provides a method to reduce or prevent the formation of UV induce a skin cancer by the application of an excipient in combination with an aminothiol or an aryl amide.

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REDUCTION OF UV INDUCED SKIN CANCER

BY TOPICAL AMINES

RELATED APPLICATIONS

The present application claims the benefit of the filing dates under 35 U.S.C. § 119(e) to provisional U.S. Patent Application serial no. 60/069,713 filed on December 15, 1997, and provisional U.S. Patent Application serial no. 60/091464 filed on July 1, 1998, both of which are hereby incorporated by reference.

FIELD OF INVENTION

The present invention is for pharmaceutical compositions for dermal delivery of amine compounds to prevent UV induced skin cancer or other UV induced dermal lesions.

This invention relates to a method for reducing the incidence of UV induced skin cancer using amine compounds which prevent radiation and chemically induced cell and DNA damage. It further relates to the method of topical administration of amine compounds to prevent UV induced malignancies.

Particularly, the present invention is for pharmaceutical compositions of aryl amides and aminothiols compounds for dermal delivery to prevent ultraviolet (UV) induced skin cancers and/or other UV induced dermal lesions.

BACKGROUND OF THE INVENTION

Chemoprevention, in its broadest sense, is the prevention of mutational events that may lead to the carcinogenic process through the use of inhibitory chemical agents, especially in high risk, disease-free individuals.

The aminothiol, S-2-(3-aminopropylamino) ethanthiol, known as WR-1065 or Ethiol™, commercially available from Alza located in Palo Alto, California, and its thiophosphate, S -2(3-aminopropylamino) ethyl phosphorothioic acid, known as WR-2721, are chemopreventive agents used

to prevent secondary tumors resulting from chemotherapy and high energy radiation therapy.

WR-1065 has the structure H_2N-$(CH_2)_3$-NH-$(CH_2)_2$-SH and was developed at the Walter Reed Army Institute of Research. WR-2721 has the structure $H_2N(CH_2)_3NH$ $(CH_2)_2$-S-PO_3H_2 and was also developed at the Walter Reed Army Institute of Research.

Aminothiols are believed to prevent DNA damage as free radical scavengers and, at lower systemic doses, facilitate the DNA repair processes. Aminothiols are known to reduce mutations, and have in some cases demonstrated the ability to inhibit early stages of carcinogenesis in animals.

Specifically, WR-1065 has been shown to be anti-mutagenic and anti-neoplastic when given by injection before and after high energy ^{60}Co gamma-ray irradiation. Low dose of WR-2721 is effective in cell culture to inhibit high energy irradiation induced mutagenesis. It is believed that aminothiols, by virtue of their polyamine-like structure, can stabilize DNA so as to facilitate the repair of potentially mutagenic lesions. WR-1065 and WR-2721 bind directly to DNA and interact with chromatin which could lead to stabilization and slowing of cell replication which would appear to facilitate DNA repair before the cell cycle irreversibly "fixes" DNA damage. Aminothiols protect against free radical damage. Aminothiols have been administered systemically before or after high energy irradiation therapy or chemotherapy to prevent DNA damage or therapy induced secondary tumors.

WR-1065 has been orally or intravenously administered to cancer patients to prevent secondary tumors. Aminothiols have been administered by injection or orally to import significant concentration of aminothiols in the blood circulation, yet the concentration in the skin is negligible.

Several amino compounds have been shown to prevent or block steps that could lead to malignant transformation. Examples of such amino compounds are aminothiols, which are also known as S-2-[3-aminopropylamino] ethyl dihydrogen phosphorothioate, amifostine, ethiofos, Ethiol®, NSC 296961, WR-2721. Ethiol, an aminothiol (also known as WR-1065, S-2-(3-aminopropylamino) ethanthiol and its thiophosphate [WR-2721]),

is as a chemopreventive agent to reduce secondary tumors during high energy γ-irradiation or chemotherapy. When ingested or injected, these compounds have been shown to cause sever side effects, including nausea and vomiting. Due to the toxic nature of these therapeutic compounds the blood levels must be kept low; however, at low blood levels essentially no dermal levels will be detected.

Aminothiols and its derivatives reduce damage to DNA and tissue, thus aiding in the reduction of malignant transformation due to ionizing radiation (i.e. ϒ-rays for cancer therapy) and chemotherapeutic agents which damage DNA.

The aryl amide, benzamide, has been shown to inhibit UV induced transformation of normal human diploid fibroblasts and hamster embryo cells at a concentration of 1 millimolar. Moreover, benzamide has been shown to inhibit chemical carcinogenesis in vitro. The efficacious dosage range is too narrow to be maintained by systemic blood routes. A narrow window of 0.1 to 15 millimolar has been reported for in vitro studies. At 0.1 millimolar, approximately 8 micromolar is achieved in the cell.

The probable mode of action of arylamides is to temporarily inhibit poly(ADPribose)polymerase resulting in a non toxic delay of cells in early S phase (prior to DNA synthesis), allowing for sufficient time for the DNA repair enzymes to repair DNA damage prior to DNA replication. If DNA damage is not repaired, a point mutation may occur during synthesis. The chemical structure of benzamides are such that benzamide would freely transverse skin to protect the dermal basal layer of the skin.

The dermal application of these anticarcinogens will result in 300 to 1000 fold less chemical in circulation than when the chemical is injected or given orally. For aminothiols to achieve a skin concentration which would be efficacious in preventing skin cancer, the orally administered systemic levels of the drug would be toxic or irritating and, if not toxic, would fail to provide continuous, efficacious concentrations of the drug to the skin. Further, systemic dosages of aminothiols have adverse side effects such as nausea,

vomiting, and weakness. Therefore, systemic dosages of aminothiols have not been used in the prevention of skin cancer.

The current invention is a novel use of aminothiols or arylamides as a topical agent to prevent skin cancer without subjecting the sun bather to the toxic side effects of either agent, administered orally. Dermal administration will enable low concentrations of these classes of anticarcinogens in the dermal layers without significant blood levels that are toxic.

SUMMARY OF THE INVENTION

The present invention provides a novel and nonobvious solution to the problem of utilizing chemopreventive compounds, such as aminothiols and aryl amides, to aid in the prevention of skin cancer. The topical dermal pharmaceutical of the present invention provides a new and useful product and method for the prevention of skin cancer without the side effects of nausea, vomiting, and weakness.

The present invention provides a topical dermal pharmaceutical composition for the reduction of skin cancer comprising:

an excipient, and

a compound of the formula (I):

$R'_2N\text{-}(CH_2)_m\text{-}NH\text{-}(CH_2)_n\text{-}SR''$

wherein

R' is a hydrogen, alkyl or aromatic group,

m is an integer from 2 to 6,

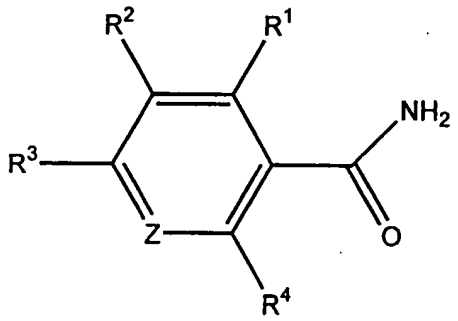
n is an integer from 2 to 6, and

R" is a hydrogen, alkyl, aromatic, or phosphoric acid group.

Further, the present invention provides a pharmaceutical composition for reducing ultraviolet light induced skin cancer comprising:

an excipient, and

a compound of the formula (II):



wherein R^1 through R^4 are hydrogen, alkyl, or an aromatic group, and Z is carbon or nitrogen.

The present invention is also directed to a method for reducing ultraviolet light induced skin cancer comprising the step of applying for delivery into the dermal layers a topical formulation containing a compound of the formula (III):

$R'_2N\text{-}(CH_2)_m\text{-}NH\text{-}(CH_2)_n\text{-}SR''$

wherein

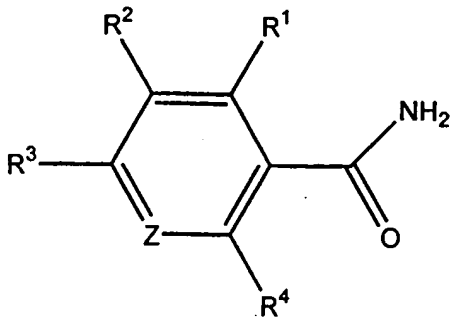
R' is a hydrogen, alkyl or aromatic group,

m is an integer from 2 to 6,

n is an integer from 2 to 6, and

R" is a hydrogen, alkyl, aromatic, or phosphoric acid group.

Additionally, the present invention is further directed to a method for reducing ultraviolet light induced skin cancer comprising the step of applying for delivery into the dermal layers a topical formulation containing a compound of the formula (IV):



wherein R^1 through R^4 are hydrogen, alkyl, or an aromatic group, and Z is carbon or nitrogen.

Therefore, an advantage of the present invention is to provide the chemical prevention of skin aging and malignant or benign cell transformation by using therapeutic compounds at low concentrations in the dermal layer, with essentially no systemic concentrations.

The further advantage of the present invention is to use dermal transport enhancers to govern the delivery rate and dermal concentration of amine compounds. An advantage of this invention is to provide a pharmaceutical composition for dermal layer delivery of an amine, particularly an aryl amide compound or its derivatives or an aminothiol and its derivatives, to prevent or reduce UV induced skin cancer. A further advantage is to provide a percutaneous penetration enhancer for use in the dermal layer delivery of amines, particularly aminothiols and arylamides.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition in the form of an excipient in combination with an amine to prevent or reduce UV induced skin cancer. The protection granted by the excipient in combination with the amine will apply regardless of application immediately before, during or immediately after exposure to UV radiation. The amine may consist of an aminothiol or its derivatives or an aryl amide or its derivatives. The excipient containing amine may also contain a dermal layer penetration enhancer or a transdermal layer penetration enhancer.

To an excipient, selected from the group consisting of a lotion, cream, or other skin softening material, is added an effective amount of an amine compound. The amine compound is selected from the group consisting of aminothiols and aryl amides. An effective amount of an amine compound is optimal to reduce the occurrence of skin cancer or other lesions but has no pharmacological, efficacious circulating concentration.

The amine compound may be of a compound of the formula (I):

$R'_2N-(CH_2)_m-NH-(CH_2)_n-SR''$

wherein

R' is a hydrogen, alkyl or aromatic group,

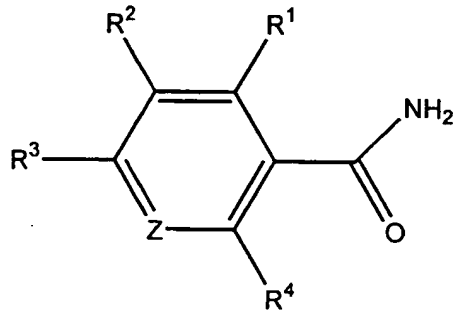
m is an integer from 2 to 6,

n is an integer from 2 to 6, and

R" is a hydrogen, alkyl, aromatic, or phosphoric acid.

In one embodiment, the compound of formula I is S-(3aminopropylamino) ethanthiol. In yet a further embodiment, the compound of formula I is S-2(3aminopropylamino) ethyl phosphorothioc acid. In yet a further embodiment, the compound of formula I is selected from the group consisting of S-2-[3-aminopropylamino] ethyl dihydrogen phosphorothioate, amifostine, and ethiofos.

In yet a further embodiment, the amine may a compound of the formula (II):



wherein R^1 through R^4 are hydrogen, alkyl, or an aromatic group, and Z is carbon or nitrogen. In yet a further embodiment, the compound of formula II may be benzamide. In another embodiment, the compound of formula II is nicotinamide.

In one embodiment, a percutaneous penetration enhancer may include compounds such as menthol to facilitate the absorption of a amino compound. Further, in yet another embodiment, the percutaneous penetration enhancer is selected from the group consisting of dimethyl sulfoxide, menthol, lauryl alcohol, lauric acid, arachidonic acid and C_{10}-C_{20} polyhydroxy acids and thymol.

Aminothiols are compounds that lend themselves to transdermal absorption. However, transdermal absorption will depend on the balance between excipients (creams, emulsifiers, and oils) and dermal absorption enhancers (i.e., menthol). Active derivatives of aminothiols are mixed with excipients and enhancers to provide a water-in-oil emulsion that is water resistant, sweat proof, and smooth to the feel.

An aryl amide is an aromatic ring system to which an amide moiety is attached. The current disclosure incorporates WR-1065 or aminothiol derivatives in a lotion for transdermal drug delivery of aminothiols, thus establishing a concentration gradient in the dermus where skin cancer initiates. Dermal absorption does not yield a significant concentration of aminothiols in the blood. WR-1065 (or derivatives of these), incorporated in a lotion formulation, will protect against UV carcinogenesis when applied before, during or after sun irradiation.

Additional additives may include in the water-in-oil emulsion (lotion) active aminothiols, adjustable SPF sun blockers, organo-modified silicone based emulsifiers (1-5% Cetyl dimethocone wax), or transdermal enhancers.

The present invention teaches a novel method of preventing cancer due to exposure to UV rays of the sun. In one embodiment, the method for reducing ultraviolet light induced skin cancer comprises the step of applying

for delivery into the dermal layers a topical formulation containing a compound of the formula (III):

$R'_2N-(CH_2)_m-NH-(CH_2)_n-SR''$

wherein

R' is a hydrogen, alkyl or aromatic group,

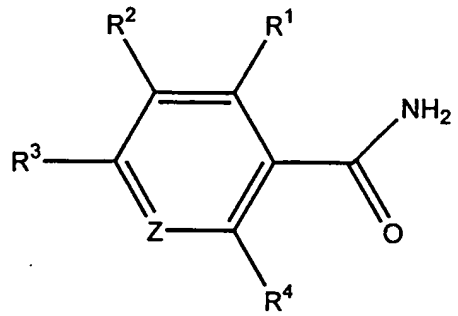
m is an integer from 2 to 6, and

n is an integer from 2 to 6, R" is a hydrogen, alkyl, aromatic, or phosphoric acid.

In one manner of the method, the compound of formula III is S-2(3-aminopropylamino) ethanthiol. In yet another practice of the method, the compound of formula III is S-2(3-aminopropylamino) ethyl phosphorothioic acid.

In one embodiment, a percutaneous penetration enhancer may be added to the topical formulation containing a compound of formula III. In yet one embodiment, the percutaneous penetration enhancer is selected from the group consisting of dimethyl sulfoxide, menthol, lauryl alcohol, lauric acid, arachidonic acid, C_{10}-C_{20} polyhydroxy acids, and thymols.

In still a further embodiment of the practice of the method for reducing ultraviolet light induced skin cancer comprises the step of applying for delivery into the dermal layers a topical formulation containing a compound of the formula (IV):



wherein R^1 through R^4 are hydrogen, alkyl, or an aromatic group, and

Z is carbon or nitrogen. Further, the method may including the step of adding a percutaneous penetration enhancer to the topical formulation containing a compound of formula IV. In one embodiment, the percutaneous penetration enhancer is selected from the group consisting of dimethyl sulfoxide, menthol, lauryl alcohol, lauric acid, arachidonic acid, C_{10}-C_{20} polyhydroxy acids, and thymols.

In yet a further embodiment of the method, the compound of formula IV is benzamide. In yet another embodiment of the method the compound of formula IV is nicotinamide.

The following table provides some examples of aminothiols.

TABLE 1

Aminothiols and some derivatives thereof comprise:

General Aminothiol Formula

$R'_2N-(CH_2)_m-NH-(CH_2)_n-SR''$

wherein

R' is a hydrogen, alkyl or aromatic group,

m is an integer from 2 to 6,

n is an integer from 2 to 6,

R" is a hydrogen, alkyl, aromatic, or phosphoric acid.

Specific Aminothiol Examples

1. $NH_2\ (CH_2)_3\ NH\ CH_2\ CH_2\ SH$
   2-[(aminopropyl) amino] ethanethiol
   WR-1065

2. $NH_2\ (CH_2\ )_3\ NH\ CH_2\ CH_2\ S\ PO_3\ H_2$
   S-2-(3-aminopropylamino) ethyphosphorothioic acid

WR-2721

3. N_2 N $CCOH_2$ NH CH_2 CH_2 –SH (CH_3 0 SO_3 H_2)
3-[(2-mercaptoethy) amino] propylonamide p-toluenesulfonate
WR-2529
H_2N-$(CH_2)_3$ -NH – $(CH_2)_2$ -$(CH_2)_2$ -S-S- $(CH_2)_2$ - NH-$(CH_2)_3$ - NH_2

4. H_2 N CH_2 CH(OH) CH_2 SPO_3 H_2
S-1-(2-hydroxy-3-amino) propyl phosphorothioic acid
WR-77913

5. CH_3 $NH(CH_2)_3$ NH CH_2 CH_2 SH
2-[3-(methylamino) propylamino] ethanethiol
WR-255591

6. H_2 N CH_2 SPO_3 H_2
S-1-(aminoethyl) phosphorothioic acid
WR-638

7. CH_3 NH $(CH_2)_3$ $NHCH_2$ CH_2 SPO_3 H_2
S-[2-(3-methylaminopropyl) aminoethyl] phosphorothioate acid
WR-3689

These and other advantages of the present invention will become apparent from considering the following description of preferred embodiments, examples, and claims described below. It is envisioned that derivatives of the aminothiols and benzamides of the present invention are encompassed by the disclosure.

EXAMPLES

EXAMPLE 1

WR 1065, or an active aminothiol derivative, may be dissolved at 0.05 to 5.0% in saline (68.4% water plus 0.8% sodium chloride). The percent of saline should be diminished by the percent of WR1065 added.

The following chart shows the compounds to be used and in a preferred embodiment of the formulation:

Compound	Percentage
WR1065	0.001 to 10.0%
ABIL WE-09	5
ABIL wax 9801	1
octyl stearate	2
cyclomethacone	3
octyl palmitate	3
caprylic/capric triglycerides	3
polydecene	2
octyl methoxycinnamate	3
octyl salicylate	3
hydroxyethyl cellulose	0.8
titanium dioxide [40% aqueous dispersion]	0 to 5%

These compounds may be added to the dissolved WR-1065. Mild homogenization may be preformed by mechanical blending at 25°C for approximately two hours to obtain sufficient blending. This gives an SPF (Sun Protective Factor) of 30. The amount of titanium dioxide may be halved to produce a likewise titanium dioxide reduction in SPF protection. The steps outlined in this Example would result in a stable water-in-oil emulsion with good stability to heat and temperature degradation. In a preferred embodiment, ABIL WE-09 and ABIL wax 9801, both obtainable from Goldschmidt of Germany, may be used along with other emulsifiers known to one skilled in the art to create a water-in-oil emulsion.

EXAMPLE 2

0.8gm of NaCl may be dissolved in 64.2gm distilled water. 5.0gms WR1065-HCl may be added and the mixture and agitated to dissolve. 5.0gms ABIL WE-09 may then be added and blended. Then, 1gm ABIL wax 9801 may be added during continuous agitation. 2gms octyl stearate, 3gms cyclomethacone, 3gms octyl palmitate, 3gms caprylic/capric triglycerides, 2gms polydecene, 3gms octyl methoxycinnamate, 3gms octyl salicylate, 5gms of a 40% dispersion of titanium dioxide in water and 0.8gms hydroxymethyl cellulose may be added. The mixture may then be stirred at 25°C for several hours and tested for one phase with microscopic examination. The resulting mixture may then be checked for smooth "feel".

EXAMPLE 3

An oil-in-water emulsion could also be utilized. An example of a lotion of this sort containing WR1065 is as follows:

Agent	Percentage
WR1065	0.001 to 10
PVP/eicoseno copolymer	5
triethanolamine	1
dimethicone	2
carbimer	2
cetyl alcohol	2
DEA cetyl phosphate	2
isopropyl myristate	2
isodecyl neopontanoate	1
rathon-CF	2
PG diocatonate	2
stearic acid	2
water	balance

The WR1065-HCR is dissolved in the water phase (13) and the PVP/eicosene copolymer added with stirring. After stirring or mixing for an interval, a

uniform suspension of fine or droplets in water should be formed. This emulsion is a lotion and the dispension, viewed under a microscope, should be relatively uniform. A smooth "feeling" lotion is obtained.

CLAIMS

1. A topical dermal pharmaceutical composition for the reduction of skin cancer comprising:

a) an excipient, and

b) a compound of the formula (I):

$R'_2N-(CH_2)_m-NH-(CH_2)_n-SR''$

wherein

R' is a hydrogen, alkyl or aromatic group,

m is an integer from 2 to 6,

n is an integer from 2 to 6, and

R" is a hydrogen, alkyl, aromatic, or phosphoric acid.

2. The pharmaceutical composition of claim 1 further including a percutaneous penetration enhancer.

3. The pharmaceutical composition of claim 2 wherein the percutaneous penetration enhancer is selected from the group consisting of dimethyl sulfoxide, menthol, lauryl alcohol, lauric acid, arachidonic acid and C_{10}-C_{20} polyhydroxy acids.

4. The pharmaceutical composition of claim 1 wherein the compound of formula I is S-2(3-aminopropylamino) ethanthiol.

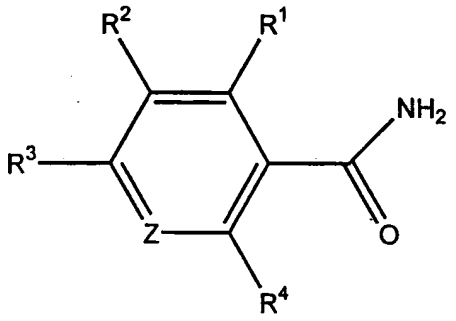
5. The pharmaceutical composition of claim 1 wherein the compound of formula I is S-2(3aminopropylamino) ethyl phosphorothioc acid.

6. The pharmaceutical compound of claim 1 wherein the excipient isselected from the group consisting of a cream, emulsifier, and oil.

7. A pharmaceutical composition for reducing ultraviolet light induced skin cancer comprising:

a) an excipient, and

b) a compound of the formula (II):



wherein R^1 through R^4 are hydrogen, alkyl, or an aromatic group, and Z is carbon or nitrogen.

8. The pharmaceutical composition of claim 7 further including a percutaneous penetration enhancer.

9. The pharmaceutical composition of claim 8 wherein the percutaneous penetration enhancer is selected from the group consisting of dimethyl sulfoxide, menthol, lauryl alcohol, lauric acid, arachidonic acid and C_{10}-C_{20} polyhydroxy acids.

10. The pharmaceutical composition of claim 7 wherein the compound of formula II is benzamide.

11. The pharmaceutical composition of claim 7 wherein the compound of formula II is nicotinamide.

12. The pharmaceutical compound of claim 7 wherein the excipient is selected from the group consisting of a cream, emulsifier, and oil.

13. A method for reducing ultraviolet light induced skin cancer comprising the step of applying for delivery into the dermal layers a topical formulation containing a compound of the formula (III):

$R'_2N-(CH_2)_m-NH-(CH_2)_n-SR''$

wherein

R' is a hydrogen, alkyl or aromatic group,

m is an integer from 2 to 6,

n is an integer from 2 to 6, and

R" is a hydrogen, alkyl, aromatic, or phosphoric acid.

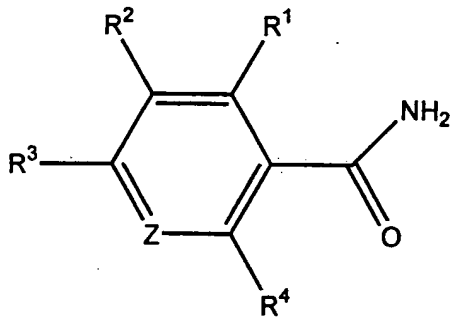
14. The method of claim 13 further including the step of adding a percutaneous penetration enhancer.

15. The method of claim 14 wherein the percutaneous penetration enhancer is selected from the group consisting of dimethyl sulfoxide, menthol, lauryl alcohol, lauric acid, arachidonic acid and C_{10}-C_{20} polyhydroxy acids.

16. The method of claim 13 wherein the compound of formula III is S-2 (3-aminopropylamino) ethanthiol.

17. The method of claim 13 wherein the compound of formula III is S-2(3-aminopropylamino) ethyl phosphorothioic acid.

18. A method for reducing ultraviolet light induced skin cancer comprising the step of applying for delivery into the dermal layers a topical formulation containing a compound of the formula (IV):



wherein R^1 through R^4 are hydrogen, alkyl, or an aromatic group, and Z is carbon or nitrogen.

19. The method of claim 18 further including the step of adding a percutaneous penetration enhancer.

20. The method of claim 19 wherein the percutaneous penetration enhancer is selected from the group consisting of dimethyl sulfoxide, menthol, lauryl alcohol, lauric acid, arachidonic acid and C_{10}-C_{20} polyhydroxy acids.

21. The method of claim 18 wherein the compound of formula IV is benzamide.

22. The method of claim 18 wherein the compound of formula IV is nicotinamide.

23. The pharmaceutical composition of claim 1 wherein the compound of formula I is selected from the group consisting of S-2-[3-aminopropylamino] ethyl dihydrogen phosphorothioate, amifostine, and ethiofos.

24. The pharmaceutical compound of claim 7 wherein the compound of formula II is selected from the group consisting of S-2-[3-aminopropylamino] ethyl dihydrogen phosphorothioate, amifostine, and ethiofos.

AMENDED CLAIMS
[received by the International Bureau on 27 May 1999 (27.05.99); original claims amended; new claims 25-27 added; remaining claims unchanged (1 page)]

25. The pharmaceutical composition of claim 1 wherein the reduction of skin cancer further comprises the reduction of ultraviolet induced wrinkles.

26. The pharmaceutical composition of claim 7 wherein the reduction of skin cancer further comprises the reduction of ultraviolet induced wrinkles.

27. The method for reducing ultraviolet light induced skin cancer of claim 13 wherein the reduction of ultraviolet light induced skin cancer further comprises the reduction of ultraviolet induced wrinkles.

28. The method for reducing ultraviolet light induced skin cancer of claim 18 wherein the reduction of ultraviolet light induced skin cancer further comprises the reduction of ultraviolet induced wrinkles.

STATEMENT UNDER ARTICLE 19

The amendments are made to clarify that the invention encompasses the reduction of ultraviolet induced wrinkles.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/27261

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/195, 31/045
US CL : 514/563, 724, 912, 563

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/563,724,912,563

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, APS, STN, SCISEARCH, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,290,813 A (CLARK ET AL.) 01 March 1994, column 3, lines 30-55.	1-5,23-24
Y	US 4,378,364 A (GRASSETTI) 29 March 1983, abstract.	1,22
Y	LIU ET AL. Repression of c-nyc gene expression by the thiol and disulfide forms of the cytoprotecter amifostine. Abstract Number 128:200628 CA. Carcinogenesis, 1997, Vol.18 (12), pages 2457-2459, see entire abstract,	1-51-6,13-17 and 23
A	PENHALIGON M. Radioprotection of mouse skin vasculature and the RIF-1 fibrosarcoma by WR-2721, Abstract Number 84243094, Int. Journal radiat. oncol. biol. phys., 1984. Volume 10/9. pages 1541-1544, see entire abstract.	1-24

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 09 FEBRUARY 1999	Date of mailing of the international search report 01 APR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer VICKIE KIM Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/27261

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	EP 0834311 A1 (ROHM AND HAAS COMPANY) 04 October 1998, Abstract and Full text.	1-24
Y	EP 0355131 B1 (PRO-NEURON, INC.) 04 September 1996, Claims 35 & 36.	1-24